REMARKS/ARGUMENTS

I. Preliminary Remarks

Claim 1-31 are pending in the application. This response is timely filed. Should any fee be deemed necessary in connection with the filing of this response, the Commissioner is hereby authorized to deduct any such fee from Marshall, Gerstein & Borun deposit account number 13-2855.

II. The Outstanding Rejections

Claims 1-3, 5-25 and 31 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of U.S. Patent No. 5,770,570 to Paul *et al.* [hereinafter "Paul"] in view of the disclosure of U.S. Patent No. 5,225,212 to Martin *et al.* [hereinafter "Martin"].

Claims 1-3, 5-25 and 31 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin, in further view of the disclosures of U.S. Patent No. 5,374,548 to Caras [hereinafter "Caras"], Noda *et al., Biochim. Biophys. Acta 1191*:324-330 (1994) [hereinafter "Noda"], and Keder *et al., J. Immunother. 16:*47-59 (1994) [hereinafter "Keder"], individually or on combination.

Claim 4 was rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin in further view of the disclosures of Caras, Noda, and Keder, and further in view of the disclosure of Kirby *et al., Bio/Technology*, November 1984, pp. 979-984 [hereinafter "Kirby"].

Claims 26-30 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin in further view of the disclosures of Caras, Noda, and Keder, and further in view of the disclosure of U.S. Patent No. 5,612,057 to Lanza *et al.* [hereinafter Lanza"].

Claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-2 and 4-6 in U.S. Patent No.

6,197,333. Likewise, claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-14 in U.S. Patent No. 6,348,214.

III. Patentability Arguments

A. The Rejection of Claims 1-3, 5-25, and 31 under 35 U.S.C. §103(a)

Claims 1-3, 5-25, and 31 were rejected, in Section 5 of the Office action, under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure Paul in view of the disclosure of Martin. The Examiner asserted that the disclosure of Paul describes liposomal compositions containing VIP to be used for the treatment of diseases such as ischemia and mental conditions. However, as noted previously by the Examiner, these liposomes are not sterically stabilized; no phospholipid component is not bound to PEG. The Examiner also asserted that the disclosure of Martin describes the preparation of liposomes wherein a lipid component is bound to a water soluble polymer, but, acknowledges that the reference does not teach that drugs can be loaded following liposome formation. The Examiner further asserted that the inclusion of PEG taught by Martin in the liposomes taught by Paul for the preparation of liposomes containing VIP and the use of these liposomes for the treatment of disease states, such as ischemia, would have been obvious to one of ordinary skill in the art. In response, the Applicants respectfully traverse.

A rejection under § 103(a) requires (1) that each element of the rejected claim be found in the art, (2) that there be a motivation to modify the prior art disclosure to arrive at the claimed subject matter, and (3) that there be a reasonable expectation of success upon combination. M.P.E.P. § 2142. The rejection of the pending claims under § 103(a) over Paul in view of the disclosure of Martin, individually or taken together, does not satisfy that standard.

The disclosure of Paul describes liposomal compositions containing VIP to be used in the treatment of diseases, but is silent with respect to VIP with a sterically stabilized liposome. Paul also incorporates VIP into the liposome during the process of making the liposome, but, as noted by the Examiner, Paul does not disclose the addition of VIP after the formation of the liposomes. The present invention differs in that liposomes prepared in the recited method include lipids covalently bound to a water soluble polymer, and after formation of these liposomes, an amphipathic peptide drug is actively loaded in a biologically

active conformation. Preparation of liposomes in this manner therefore requires the amphipathic compound to first traverse the polymer region of the liposome exterior, then interact with the lipid bilayer, and finally acquire a biologically active conformation once in the bilayer. Whether or not all of this can be accomplished is simply not predictable from the disclosure of Paul. For example, there is no way to predict if PEG will interfere with the ability of the amphipathic compound to interact with the liposome, or even if is does not, whether the amphipathic compound will acquire a biologically active conformation once so associated. More importantly, if these two steps are accomplished, it is impossible to predict if the amphipathic compound in the lipid bilayer will be able to interact with its receptor in the polymer environment on the liposome exterior.

The disclosure of Martin adds nothing to this lack of predictability of success. Martin describes preparation of liposomes wherein a lipid component is bound to a water-soluble polymer, but is silent with respect to any method of loading vesicles with drugs after liposome formation as is taught in the present invention. In Martin, the amphipathic compounds are encapsulated within the liposome, unlike the present invention. Like Paul, the liposomes of Martin are wholly distinct from those prepared in the present invention and even if the disclosure of Martin is added to that of Paul, it would be impossible to predict whether the addition of an amphipathic compound to a preformed sterically stabilized liposome would even permit loading of the amphipathic compound in a useful form. Accordingly, neither Paul nor Martin disclose or suggest that loading a compound to a preformed sterically stabilized liposome is desirable or even attainable.

In further support of his argument, the Examiner cited the new reference of Tagawa *et al.*, U.S. Patent No. 5,264,221 [hereinafter "Tagawa"] which allegedly discloses the retention of the functional ability of monoclonal antibodies attached to the surface of PEGylated liposomes. The Applicants submit that the liposome compound described by Tagawa is unlike the present invention because an antibody is a large molecule, generally 150 kDa molecules or larger, attached to the surface of a liposome, whereas, VIP is approximately 3 kDa. Accordingly, even if a large protein is able to associate with a sterically stabilized liposome and interact with it's receptor/antigen through the polymer environment, it cannot be predicted whether a small protein, here approximately one-fiftieth the size of an antibody, can do the same. In addition, an antibody is a water-soluble protein which circulates in an active conformation, whereas the present method requires an

amphipathic compound, having both hydrophobic and hydrophilic regions thereby reducing the percentage of molecules having an active conformation in an aqueous environment, to associate with the liposome and acquire an active conformation.

Finally, the Examiner has asserted that the Applicants have not demonstrated unexpected results in the treatment of various claimed disease states using the methods of the invention as opposed to prior art processes. The Applicants submit that they need not show unexpected results in the outcome of the treatment of the various claimed diseases using the claimed methods in view of the fact that the Examiner has failed to establish a reasonable expectation of success on the part of the skilled worker to make the invention as presently claimed. Indeed, the Applicants need only to show that the recited sterically stabilized liposomes can be used for the delivery of biologically active VIP, which has been done.

The method of the present invention therefore includes the use of a liposome composition, the production of which includes a variety of obstacles that the art fails to address. The Applicants submit that, in view of these obstacles and the unpredictability of success arising therefrom, the skilled worker would have to actually reduce the invention to practice to ever determine if the method would in fact work. Accordingly, any degree of success cannot be predicted beforehand, thereby precluding any assertion of obviousness. As a result, the rejections of claims 1-3, 5-25, and 31 under §103(a) must be withdrawn.

B. The Rejection of Claims 1-3, 5-25, and 31 under 35 U.S.C. §103(a)

Claims 1-3, 5-25, and 31 were rejected, in Section 6 of the Office action, under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure Paul in view of the disclosure of Martin and further in view of the disclosures of Caras, Noda, and Keder, individually or taken together. The disclosures of Paul and Martin are set out above in Section III A. The disclosure of Caras is asserted to demonstrate that drugs can be loaded on a preformed liposome, and, similarly, the disclosure of Noda is asserted to disclose that VIP can be loaded on preformed liposomes. The disclosure of Keder was cited for describing a process of preparation of liposomes and incubating the liposomes (i.e., loading) with IL-2. The Examiner asserted that it would have been obvious to one of ordinary skill in the art to add a drug to the preformed liposomes of Martin with the expectation of obtaining similar results since Martin teaches that liposomes can be made by

any art known method, and the references of Caras, Noda, and Keder show that the liposome formulations and technique of such loading are art known. In response, the Applicants respectfully traverse.

The rejection of the pending claims under § 103(a) over Paul in view of the disclosure of Martin and further in view of the disclosures of Caras, Noda, and Keder, individually or taken together, does not satisfy the standard for obviousness set out in Section III A above. For reasons set out above, neither the Paul nor the Martin disclosures (with or without the disclosure of Tagawa) provide the worker of skill in the art with any expectation of success with the present invention and the disclosure of Caras, Noda, and Keder as discussed below fail to rectify this deficiency. Caras simply describes covalently attaching to a preformed liposome a compound with a glycophosatidylinositol (GPI) signal; however, the Caras disclosure is silent with respect to use of sterically stabilized liposomes in this process. It is unpredictable if Caras would in fact be able to covalently attach this GPI signal to a sterically stabilized liposome. Noda describes loading of VIP to a preformed liposome, but the disclosure does not suggest the use of sterically stabilized liposomes and fails to add anything to the disclosures of Paul and Martin. Moreover, Noda is silent as to whether the resulting VIP/liposome compositions are biologically active (with respect to the ability of VIP to bind to its receptor). Keder discloses the encapsulation of compounds, i.e. IL-2, within liposomes, but there is no discussion of loading compounds to the already formed liposome. Thus, none of the cited references, alone or in combination, teaches or suggests that loading a compound to a preformed sterically stabilized liposome would result in a biologically active product.

The combined disclosures of the cited references in this rejection are no different from the disclosures of Paul, Martin, and Tagawa. One of the essential features of the present invention is that the liposomes must be sterically stabilized (wherein at least one lipid component of the bilayer is attached to a water soluble polymer). Moreover, the resulting liposome must be *biologically active* with respect to the compound that is subsequently loaded. Polymer attachment to a liposome necessarily gives rise to steric hindrance, as well as physical changes in the localized environment at the immediate exterior of the liposome. Whether or not a compound residing in this polymer-rich environment would maintain a proper biological conformation, or be able to interact with a biological ligand, is not predictable, and neither Noda nor Caras suggests that such a liposome

composition would be biologically active. As a result, and for reasons discussed above, the worker of ordinary skill would not be able to predict beforehand whether the present claimed invention would be have any utility, i.e., be biologically active, without making and testing the liposome composition. Accordingly, success can only be demonstrated and is not predictable beforehand.

As a result, the rejection of claims 1-3, 5-25, and 31 under §103(a) is improper and must be withdrawn.

C. The Rejection of Claim 4 under 35 U.S.C. §103(a)

Claim 4 was rejected, in Section 7 of the Office action, under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin, and further in view of the disclosures of Caras, Noda, and Keder, further in view of the disclosure of Kirby.

The disclosures of Paul, Martin, Caras, Noda, and Keder were cited for reasons described in Sections III A and B above. The Examiner asserted that the method in the disclosure of Martin does not involve dehydration and rehydration of the liposomes; however, the Examiner asserted that Kirby teaches a method of preparation of liposomes by dehydrating the lipid vesicles and then rehydrating them, resulting in uniform-sized liposomes and that the method is simple and can be used on an industrial scale. Therefore, the Examiner asserted that the introduction of the dehydration-rehydration procedure in the method of preparation of liposomes of Martin would have been obvious to one of ordinary skill in the art because of the advantages of such a step taught by Kirby. The Applicants respectfully disagree.

The standard for a rejection under § 103 is set forth in Section A above. As discussed above, none of the disclosures of Paul, Martin, Noda, Caras, or Keder suggests the liposome composition as recited in claim 4 and the disclosure of Kirby does not correct this defect. Kirby fails to disclose the use of a liposome that is sterically stabilized, much less loaded with a targeting component, such as VIP. There is also no teaching that a targeting component can be attached after the liposome is formed. Furthermore, as discussed above, the addition of polymers, i.e. PEG, to the exterior of a liposome alters the localized environment, and as a result, it would be impossible to predict whether a targeting agent in

the polymer environment would be able to identify and/or interact with its receptor and demonstrate biological activity.

The combination of the references, therefore, fails to suggest the method of claim 4. Because of the unpredictable utility of these compounds, the worker of ordinary skill would not be motivated to produce these compounds and the cited references fail to overcome this unpredictability, thereby failing to provide any expectation of success. The Applicants therefore submit that the rejection of claim 4 under §103(a) is improper and must be withdrawn.

D. The Rejection of Claims 26-30 under 35 U.S.C. §103(a)

Claims 26-30 were rejected , in Section 8 of the Office action, under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of Paul in view of the disclosure of Martin, in further view of the disclosures of Caras, Noda, and Keder, and further in view of the disclosure of Lanza.

The Examiner asserted that the disclosures of Paul, Martin, Caras, Noda, and Keder do not teach a diagnostic method using liposomes; however, the Examiner asserted that the use of liposomes in the diagnostic methods of claims 26-30 would have been obvious to one of ordinary skill in the art, with the expectation of obtaining similar results, since the disclosure of Lanza shows the routine use of liposomes for diagnostic purposes. The Applicants respectfully disagree.

As discussed above, none of the disclosures of Paul, Martin, Noda, Caras, or Keder suggests the liposome composition as recited in claims 26-30 and the disclosure of Lanza does not correct this defect. Lanza fails to disclose the use of a liposome that is sterically stabilized, much less loaded with a targeting component such as VIP. Furthermore, there is no teaching that a targeting component can even be loaded once the liposome is formed. Also as discussed above, the addition of polymers, i.e. PEG, to the exterior of a liposome alters the localized environment, and as a result, it would be impossible to predict whether a targeting agent in the polymer environment would be able to identify and/or interact with its natural target ligand.

None of the references suggests or implies any diagnostic purposes for the liposome compositions described therein, and as a result, the cited references are wholly

unrelated to the subject matter of claims 26-30. The combination of the references, therefore, fails to suggest the diagnostic liposomes of claims 26-30. Because of the unpredictable utility of these compounds, the worker of ordinary skill would not be motivated to produce these compounds and the cited references fail to overcome this unpredictability and provide any expectation of success. The Applicants, therefore, submit that the rejection of claims 26-30 under §103(a) is improper and must be withdrawn.

E. The Rejection for Obviousness-Type Double Patenting

Claims 15-25 and 31 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-2 and 4-6 in U.S. Patent No. 6,197,333. Likewise, claims 15-24 were rejected under the judicially-created doctrine of obviousness type double patenting in view of claims 1-14 in U.S. Patent No. 6,348,214.

In response, the Applicants submit that a rejection under the judicially-created doctrine of obviousness type double patenting may only be made with a comparison of the claims in this application and the cited patents, not the specifications (*see* MPEP § 804). The claims in the cited patents, parent applications to the instant application, do not suggest the presently claimed invention, specifically because all the elements of the presently claimed invention are not found in the cited claims from U.S. Patent Nos. 6,197,333 and 6,348,214. The claims of the present invention are to methods of treatment; the claims in U.S. Patent 6,348,214 are to processes of producing; and the claims in U.S. Patent No. No. 6,197,333 are to products made by such processes.

Therefore, the rejection under the judicially-created doctrine of obviousness type double patenting is improper and should be withdrawn.

SUMMARY

In view of the amendments and remarks made herein, the Applicants believe that claims 1-31 are in condition for allowance and request expedited notification of the same.

Respectfully submitted,
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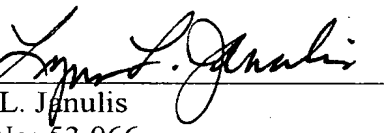
By: 
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